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Clival Chordoma: Case Report and Review of Recent Developments in Surgical and Adjuvant Treatments

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Summary

Chordomas are rare tumors that can develop anywhere along the craniospinal axis. These tumors present challenges with respect to diagnosis and treatment due to a high rate of recurrence, even after multiple surgeries, and the propensity to involve any region within the craniospinal axis. New developments in radiation therapy have improved recurrence-free survival in patients with chordomas. Different regimens of chemotherapy and molecularly-targeted therapies, as adjuvants to surgery, have been described in individual case reports and case series. The purpose of this paper is to describe a case of clival chordoma and review recent developments in diagnostic and therapeutic options.

A 77-year-old female was referred because of diplopia and progressively worsening headaches. Head imaging revealed a large expansile and erosive mass in the skull base. The patient underwent a successful endoscopic endonasal trans-sphenoidal resection of the mass, with biopsy confirming the diagnosis of chordoma. Postoperatively, the patient experienced an improvement in neurological symptoms.

Chordomas can present a diagnostic challenge due to the rare occurrence and a tendency to involve any region within the craniospinal axis.

MeSH Keywords:

Chemoradiotherapy • Chondrosarcoma • Chordoma • Skull Base • Skull Base Neoplasms

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Background

Chordomas, which are remnants of the notochord, originate from the bone and can occur anywhere along the craniospinal axis. The incidence rate of chordomas is 0.08 per 100,000, with a higher incidence rate of 0.1 in males, versus 0.06 in females. These tumors are rare in patients younger than 40 years [1]. About 32% of chordomas occur intracranially, 32.8% are spinal and 29.2% sacral [1]. Chordomas can present a diagnostic challenge due the rare prevalence and a tendency to involve any region within the craniospinal axis. Similarly, their location can present a therapeutic challenge, since they may not be amenable to surgical resection. In this paper, we describe a case of clival chordoma, discuss various diagnostic modalities available to differentiate chordomas from other tumors, and describe therapeutic options including adjuvants.

Case Report

A 77 year-old female presented with a one-year long history of progressively worsening headaches, along-with a 3 month history of double vision. The headache was of a dull, aching character, fluctuated in intensity, was only partially relieved by acetaminophen, and was non-positional.

The patient was seen in the ophthalmology and neurosurgery clinics. The visual field testing and ophthalmologic exam, including a fundoscopic exam, were normal except for right abducens palsy. In the neurosurgical clinic, a neurological exam was remarkable only for the right abducens palsy.

A CT scan of the sinuses was obtained (Figure 1) which revealed a large, expansile, erosive mass within the midline

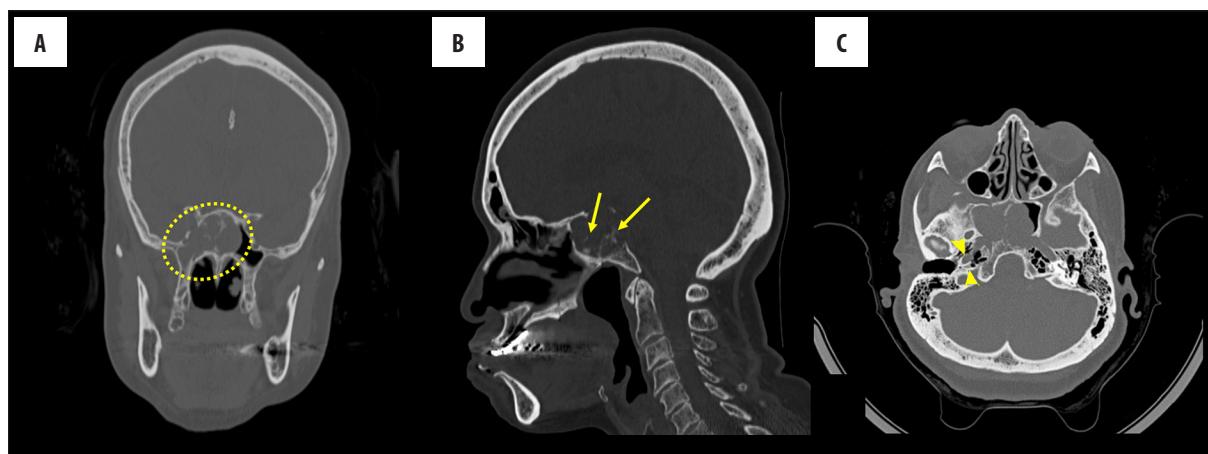


Figure 1. CT of the nasal cavity and paranasal sinuses performed without contrast. There is a large isodense mass centered in the sphenoid sinus and sella (encircled in **A**) with scattered calcifications (arrows in **B**). The mass fills the sphenoid sinus eroding it inferiorly. It extends into the right pneumatized pterygoid (arrowheads in **C**). There is also extension into the posterior fossa with effacement of the prepontine cistern and involvement of both cavernous sinuses.

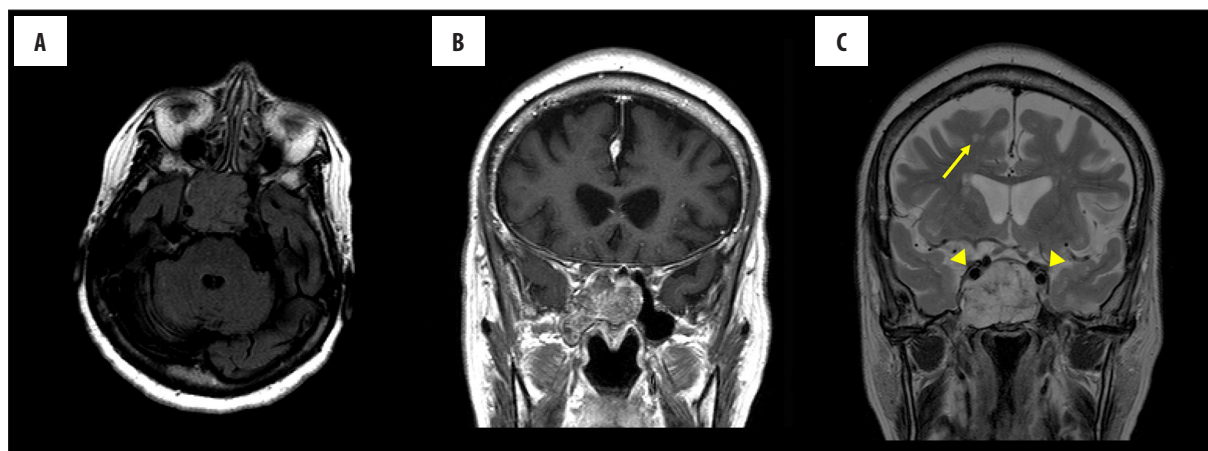


Figure 2. MRI examination of the brain and pituitary gland performed before (**A**) and after (**B**) administration of 14 ml of Magnevist intravenous contrast. A large mass involves the upper portion of clivus and the sphenoid sinuses can be observed. The mass extends to involve the pneumatized portion of the right sphenoid sinus. The internal septations correspond to the calcifications observed on the CT scan (Figure 1), suggesting an internal calcified matrix. The mass abuts both cavernous carotid arteries (arrowheads, **C**). Scattered foci of hyperintense T2 and FLAIR signals are also observed in the white matter, suggestive of mild microangiopathy (arrow in **C**).

sphenoid sinus. It measured more than 3 cm in all dimensions. The mass was isodense and filled the sphenoid sinus completely, eroding it inferiorly and extending into the right pneumatized pterygoid. The left pterygoid process was also pneumatized, but did not accommodate the mass. The mass was also eroding into the superior aspect of the clivus, and extended into the posterior fossa. It had scattered calcifications, which likely represented erosion of the native bone. Brain MRI performed before and after administration of 14 ml of contrast (Magnevist) revealed a large mass involving the clivus and the sphenoid sinus, predominantly on the right and with the same characteristic findings as on CT (Figure 2). The mass was hyperintense on T2-weighted images, mildly hypointense on T1-weighted images, and showed heterogeneous enhancement.

The patient underwent endoscopic endonasal trans-sphenoidal skull base surgery with total resection of the mass. The diagnosis was confirmed with a perioperative biopsy result, which showed lobules separated by collagenous

bands, enclosing physaliphary cells in a myxoid matrix. The physaliphary cells were glycogen and mucin-laden, thus classifying it as a conventional chordoma.

After surgery, an improvement in diplopia and headache was observed. The postoperative non-contrast CT (Figure 3) of the nasal cavity and paranasal sinuses showed residual air and packing material, but no hemorrhage or abnormal fluid collections. MRI performed 2 days after resection, with and without contrast (14 ml of Magnevist), revealed a thin rim of irregularly enhancing soft tissue superiorly, most likely representing postoperative soft tissue changes or minimal residual tumor, and a hyperintense cystic mass located superiorly (Figure 4). At one-year follow-up, the patient was free of tumor recurrence.

Discussion

Chordomas can have varied presentations, depending on their location. A cranial tumor may present with chronic



Figure 3. (A, B) CT scan of the brain performed with Stryker protocol without administration of intravenous contrast; status post trans-sphenoidal approach for resection of a large skull base mass. The mass is resected with residual air and packing material observed.



Figure 4. MRI of the brain obtained using a pituitary protocol, 14 ml of Magnevist was administered; status post trans-sphenoidal resection of a large mass at the skull base. A thin rim of irregularly enhancing soft tissue is observed at the resection site, most pronounced superiorly. A T2 hyperintense signal is observed (arrow) without enhancement and likely represents cystic changes.

intractable headaches, cranial neuropathy (as in our patient who had right abducens palsy), and other rarer symptoms such as subarachnoid hemorrhage, cerebrospinal fluid rhinorrhea, and epistaxis [2]. Tumors located along the spine may result in back pain (which may be dermatomal in nature), sphincter dysfunction, lower extremity weakness, and paresthesias. Various imaging modalities assist in the differential diagnosis. Plain radiographs may reveal local bony erosion and scattered calcifications. On CT, chordomas have decreased attenuation and hyperdense regions, may demonstrate erosion of nearby structures and exhibit an inner calcified matrix. On brain MRI, bony expansion is

a typical feature, along with hypointensity on T1-weighted images and hyperintensity on T2-weighted images. There may be a heterogeneous enhancement pattern on T1-weighted images after administration of gadolinium. Final diagnosis can only be made based on a perioperative biopsy, using various analytical techniques. The differential diagnosis and the distinguishing features of masses in the skull base are listed in Table 1.

Table 1. Imaging characteristics of various tumors at the skull base.

Diagnosis	Plain radiograph	MRI	CT
Chondrosarcoma	May appear translucent and expansile with matrix calcifications. About half are lytic. Endosteal scalloping may be seen	Lesions are lobulated and have low signal on T1- and high intensity on T2-weighted sequences. Heterogeneous enhancement with contrast. Calcifications may appear as signal voids	May appear as a translucent soft tissue mass with matrix calcifications, endosteal scalloping, and exhibit heterogeneous enhancement with contrast
Pituitary macroadenoma	Unable to identify soft tissue mass	Appears isointense on T1 and T2, but posterior lobe may be hyperintense on T2. Moderate enhancement seen on gadolinium contrast. Imaging mode of choice	Appears solid and isodense to brain, rare calcifications, may involve adjacent bony components
Chordoma	Unable to identify soft tissue masses but can show lytic lesions with irregular calcifications	Low signal is observed on T1 with areas of high signal intermixed that may represent hemorrhage. High signal on T2. Heterogeneous enhancement is seen after administration of gadolinium. Differentiation from chondroma may be challenging	Appears as an isodense, well-demarcated soft tissue mass that is lytic and locally destructive. Has irregular calcifications, and heterogeneous contrast enhancement. Destruction of several vertebrae may be seen in case of spinal involvement
Osteosarcoma	A soft tissue mass causing bony destruction is seen. Periosteal and lamellated reaction are also sometimes visualized. Variable calcification can be observed	The best imaging modality to assess local spread, soft tissue involvement, and tumor extension. The soft tissue component has intermediate signal on T1 and high signal on T2. Solid components typically enhance with contrast on T1	May assist in diagnosis, when plain radiographs are unclear. Especially useful for identifying mineralized bony matrix which can be missed on plain radiographs and MRI
Hemangiomas	Vertebral hemoangiomas have thickened vertical trabeculation; Calvarial hemangiomas are osteolytic and have trabeculae in a “sun-burst” pattern	Hyperintense signal on T2-weighted MRI corresponds to increased vascularity. Hypointense signal on both T1 and T2 is characteristic of thickened vertebral trabeculae	Thickened vertebral trabeculae are seen in better detail than on plain radiographs. Bony destruction may be seen

Histopathology

Chordomas can be divided into three different types. Conventional chordomas are slow-growing tumors that have physaliphary cells within a myxoid stroma and may show cellular proliferation, as evidenced by numerous mitoses, nuclear pleomorphism, and presence of nucleoli [3]. These demonstrate reactivity for the S100 protein, epithelial membrane antigen, vimentin, and cytokeratins. The chondroid variety shows areas of chondroid differentiation within an otherwise histologically indistinct conventional chordoma [3]. The dedifferentiated variety exhibits a high-grade sarcoma in combination with conventional or chondroid chordoma, and may be associated with a worse prognosis than other subtypes [3]. The dedifferentiated component is rapidly growing, can lead to metastatic spread, and signals disease progression [4].

Brachyury is a transcription factor that is involved in notochord development and is a very specific marker for both

notochord and notochord-derived tumors [5]. Brachyury has been shown to be expressed in all chordomas investigated in a study including both chondroid and chondroid components, whereas it was not detected in any of the other analyzed tumors [5]. Chondrosarcoma does not express brachyury and therefore this biomarker can be used to distinguish chordoma from chondrosarcoma. Brachyury expression is also used to distinguish chordoma from germ cell tumors and metastatic clear cell renal carcinoma [6]. Brachyury is not detected in nucleus pulposus, which could suggest a different origin for nucleus pulposus than notochord alone [5]. Presence of MIB1 and p53 staining also has diagnostic and prognostic significance, indicating proliferative activities in chordomas as well as other central nervous system tumors [7], with MIB1 closely following p53 expression [8]. Epidermal growth factor receptor (EGFR) expression has been found in 69% of chordoma cases, and tyrphostin (EGFR inhibitor) reduced proliferation of a chordoma cell-line *in-vitro*; hence, EGFR is a potential therapeutic target [9]. Other molecular markers

within chordomas have been investigated, such as AKT, mTOR, and TSC; it was noted that 65% of chordomas that were studied may respond to mTOR and AKT inhibitors [10]. Genetic analysis also offers significant prognostic information. *De novo* chordomas with a normal karyotype were noted to have a recurrence rate of only 3% in a study investigating karyotypes of chordomas from 64 patients, whereas an abnormal karyotype resulted in a recurrence rate of 45% and signaled disease progression and poor outcomes [11]. The most important karyotype abnormalities are duplications on 6q27 and brachyury gene [11].

Medical treatment

Imatinib, a tyrosine kinase inhibitor currently approved as monotherapy for chronic myelogenous leukemia, has been investigated in chordomas, and its use has been associated with tumor liquefaction and a decreased density of chordomas expressing the platelet-derived growth factor receptor-beta (PDGFRB) [12]. It has also proved efficacious in treatment of clival metastases from other tumors. For instance, in a patient with a clival metastasis of gastrointestinal stromal tumor, treatment with imatinib resulted in decreased diplopia [13]. In a phase-II study, of 50 patients with PDGFRB positive chordomas who received imatinib, 35 patients had stable disease, with a clinical benefit rate of 64% and median progression-free survival of 9 months [14]. Combined use of imatinib and sirolimus (rapamycin) – an immunosuppressant that directly inhibits the mammalian target of rapamycin (mTOR), has been studied in patients with chordomas that are resistant to imatinib. In a series of 9 patients with secondary resistance to imatinib, the combined use of imatinib and sirolimus resulted in a partial response in 7 patients, stable disease in 1 patient, and progressive disease in 1 patient, with a clinical benefit rate of 89% [15]. Cisplatin has also proven efficacious in tumor response and shrinkage amongst patients who developed secondary resistance to imatinib [16]. In a report of a 19-month-old girl with malignant cervical chordoma with pulmonary metastases, a multi-agent chemotherapeutic regimen involving systemic ifosfamide and doxorubicin combined with intrathecal hydrocortisone, cytarabine, and methotrexate was found to be effective [17]. Another case report demonstrated that a different chemotherapeutic regimen consisting of isotretinoin, interferon-A, thalidomide, and doxorubicin was efficacious in slowing progression of metastatic clival chordoma [18]. Cetuximab and gefitinib have also been demonstrated to cause partial response in a patient with sacral chordoma and pulmonary metastasis, whose biopsy had shown expression of epidermal growth factor receptor [19].

Surgery

Surgical intervention is the recommended treatment modality, with an aim to achieve a gross total resection of the tumor. The endoscopic endo-nasal trans-sphenoidal approach is the preferred mode of surgery for suspected chordomas and chondrosarcomas of the clivus, as in our case [1]. This technique is minimally invasive and has an efficacy similar to open surgery for clival chordomas [20]. Other approaches have been described in the literature, including trans-mandibular, subtemporal-preauricular,

extreme lateral transcondylar, and transcochlear; however, complete resection in all cases is difficult and local recurrence may occur [21]. The primary goal of surgery is to achieve primary radical resection, followed by adjuvant treatments. This approach has been shown to improve long-term outcomes and recurrence-free rates [22,23], similar to other brain tumors such as glioblastoma multiforme, when compared to surgery alone [24]. Surgery is frequently combined with adjuvant radiation therapies such as gamma knife surgery and has been shown to result in a satisfactory long-term control of chordomas [25,26].

Radiation treatment

Radiation therapy is best offered in combination with aggressive surgical resection. Several modes of adjuvant radiation therapy have been rigorously investigated. The proton and photon beam therapies improve outcomes in patients with chordomas, chondrosarcomas, ocular malignancies, and sinonasal tumors, with a 5-year local control rate of 50-65% for photon beam and 81% for proton therapy, respectively [27]. In a study of 8 patients with chordomas or chondrosarcomas of the skull base and a median tumor volume of 40 cm³ who received a median dose of 63 Gy of proton beam therapy, a survival rate of 100% was reported with local control rate of 100% for chordomas and 86% for chondrosarcomas over a 3 year follow-up [28]. No toxicities such as optic neuropathy and brain stem injury were reported [28]. For patients with spinal chordomas and chondrosarcomas who had undergone resection, the overall survival rate was 93.3%, and local control rate was 58% at 2 years after treatment, with a median dose of 70 Gy in the case of proton therapy [25]. Proton beams have a larger mass, straighter trajectories, and more effective energy deposition than photon beams, and they cause less damage to the surrounding critical structures. Carbon ion radiotherapy has also been studied in 38 patients with sacral chordomas who had a median age of 66 years, median tumor volume of 523 cm³, received a median dose of 70.4 Gy, and had a median follow-up of over 80 months [29]. The 5-year survival rate was 86%, the 5-year local control rate was 89%, and only minimal complications were reported [29]. In a cohort of 155 patients with skull base chordomas who were treated with carbon ion irradiation at a median total dose of 60 Gy, the 10-year local control was 54% and the 10-year overall survival was 75% [30]. Experience with CyberKnife stereotactic radiosurgery has been reported in 18 patients with a median tumor volume of 128 cm³, who had received a median dose of 35 Gy and had a median follow-up of 46 months [31]. The local control rate was 59.1% at 65 months, and the survival rate was 74.3% [31].

Prognosis

The available data regarding prognosis varies and depends on the source of reports, definitions of survival and recurrence-free rates, treatment modality, and duration of follow-up. The respective survival rates at 5 and 10 years of follow-up have been estimated to be 67.6% and 39.9%, respectively in one report [1]. In another report, these figures were 47% and 27% for no treatment, 33% and 16% for surgery alone, 69% and 34% for radiotherapy alone, and 75% and 59% for combination therapy [24]. As more

treatment modalities are developed and longer-term follow-ups are available, the survival rates are likely to change.

Conclusions

Chordomas are rare tumors of a notochordal origin that often have an insidious onset. As they progress, they cause local destruction, and hence neurological deficits. Early diagnosis is essential, as aggressive surgical resection followed by adjuvant therapy improves long-term outcomes. In this review, we described a case of clival chordoma and discussed various diagnostic methods to differentiate

chordomas from other tumors on imaging and on histopathology. Moreover, we reviewed various modes of treatment including the necessity for primary radical resection in combination with adjuvant treatment. Treatment modalities are likely to evolve, as new literature emerges on the efficacy of chemotherapy and novel modes of radiation therapy, with the hope to achieve better overall survival rates.

Disclosures

The authors report no conflicts of interest.

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